REMARKS

The title and abstract have been amended to reflect the subject matter of the instant claims.

The amendment to the title is supported, *inter alia*, by the present claims, including claim 122.

The legend of Figure 14 has been amended to refer to the specific subparts of Figure 14 and also to recite the sequence identifier (SEQ ID NO:1) of the sequence shown in Figure 14D, as well as to provide a description of Figure 14D. Support for this amendment can be found in Figure 14D itself as well as in the description of Figures 14A-14C found on page 8, lines 13-24 of the specification.

The specification has also been amended to capitalize and provide a generic description of the trademark term "Cy Dye™".

Claims 122, 178 and 185-232 are pending in the present application. Claims 122, 178, 185-188, 190-192, 194-216, 218-220, 226-228 and 232 have been amended for clarification purposes only and in no way to narrow the scope of the claims. In addition, claim 220 has been amended to correct an improper claim dependency upon a canceled claim.

Support for the amendment to claims 122 and 178 can be found, *inter alia*, at page 14, line 9-11. Support for the amendment to claim 185 can be found, *inter alia*, at page 16, lines 31 through page 17, line 29. Support for the amendment to claim 228 can be found, *inter alia*, on page 21, lines 21-23 and claims 182-184 as filed. The remainder of the claims have been amended to track the language of the claims from which they depend.

No new matter has been added by the amendments made herein. Entry of the foregoing amendments is respectfully requested.

THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

Objection To The Title

The Examiner objected to the title, "GENE DISCOVERY USING MICROARRAYS," as being not descriptive of the claimed invention. In response, Applicants have replaced the existing title with the new title, "POSITIONALLY-ADDRESSABLE ORDERED POLYNUCLEOTIDE ARRAYS." Accordingly, it is requested that the objection to the title be withdrawn.

Objection To The Abstract

The abstract has been objected to as referring to methods and systems instead of the presently claimed invention of positionally-addressable arrays. In response, Applicants have amended the abstract to reference the claimed positionally-addressable ordered arrays instead of systems and methods. Accordingly, it is requested that the objection to the abstract be withdrawn.

Objection To The Sequence Listing

The disclosure is objected to because it does not reference SEQ ID NO:1, the sequence listing submitted on paper and in computer-readable form. In response, the specification has been amended to refer to SEQ ID NO:1. Accordingly, it is requested that this objection to the disclosure be withdrawn.

Objection To The Recitation of Trademarks

The use of the trademark "Cy Dye™" is objected to because the term is not capitalized or accompanied by generic terminology. In response, the specification has been amended by replacing the term "Cy Dye™ kit" with the term "CY DYE™ labeling kit."

Accordingly, it is requested that the objection to the disclosure for the use of trademarks be withdrawn.

THE OBJECTIONS TO THE CLAIMS SHOULD BE WITHDRAWN

Claims 228-231 are objected to as being confusing. The Examiner contends that "it is confusing whether the entire sample is on the surface [of the solid support], or if just the population is on the surface, both of these are on the surface, or some other meaning is intended."

Applicants respectfully disagree and submit that one of skill in the art would understand that the claim language of claim 228 "further comprising a sample comprising a population of cellular RNA or nucleic acid derived therefrom on the surface of said solid support such that said sample is in contact with said polynucleotide probes" would clearly convey that the sample comprising the population of cellular RNA or nucleic acid derived therefrom is on the surface of the solid support, and that the sample and thus the population of cellular RNA or nucleic acid derived therefrom are in contact with the probes.

Nevertheless, without agreeing with the Examiner and merely to expedite prosecution, claim 228 has been amended to read that the array comprises "a sample on the surface of said solid support such that said sample (i) is in contact with said polynucleotide probes, and (ii) comprises a population of cellular RNA or nucleic acid derived therefrom."

It is submitted that the foregoing amendment obviates the objection to claim 228 and claims 229-231 dependent therefrom. Accordingly, it is requested that the objection to claims 228-231 be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 122, 185, 189, 192, 197, 200, 220-224, 226, and 228-232 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Claim 122

The Examiner contends that claim 122 is indefinite for the recitation of "respective genomic sequences for the probes" where the claim earlier specified that the probes comprise sequences complementary and hybridizable to different genomic sequences.

Applicants respectfully disagree and submit that one of skill in the art would understand that "genomic sequences for the probes" means "genomic sequences complementary to the probes." However, to expedite prosecution, Applicants have amended both occurrences of "genomic sequences for" the probes in claim 122 to "genomic sequences complementary and hybridizable to" the probes. For the sake of consistency, the same amendment also has been made to claims 178, 194, 195, 198, 199, 202, 203, 206, 207, 210, 211, 214, 215, 218, and 219. The rejection is thus obviated.

Claims 192 and 200

Claims 192 and 200 are also alleged to be indefinite for the recitation of "genomic sequences for each probe." Applicants respectfully disagree for the reasons explained in response to the rejection of claim 122 above; however, to expedite prosecution, Applicants have amended the recitation of "genomic sequences for each probe" in each of claims 192 and 200 to recite "genomic sequences complementary and hybridizable to each probe." For the sake of consistency, the same amendment also has been made to claims 196, 204, 208, 212, 216, and 220. The rejection is thus obviated.

Claims 122, 185, 189, 192, 197, 200, 221-224, 226 and 228-232

Claims 122, 185, 189, 192, 197, 200, 221-224, 226 and 228-232 are alleged to be indefinite because of the term "first plurality" in claims 122, 226, and 227. According to the Examiner, it is unclear what is meant by this term as only one plurality is recited in the claims.

Without agreeing with the Examiner that the term "first plurality" is unclear, Applicants have amended claim 122, 225, 226 and 227 by deleting the word "first," thereby removing all references to a "first" plurality. The rejection is thus obviated.

Claims 185, 189, 192, 197, 200, 221-224, 226 and 228-232

Claims 185, 189, 192, 197, 200, 221-224, 226 and 228-232 are rejected as indefinite because the recitation of "repetitive elements, simple repeats, or polyX repeats have been excluded" in lines 1 and 2 of claim 185 and in lines 2 and 3 of claim 232 is indefinite. The Examiner contends that these terms are not defined in the specification.

Repetitive elements, simple repeats, and polyX repeats are examples of regions of low information content provided by the specification (see discussion on page 16, line 31 through page 17, line 29 of the specification), and therefore one of skill in the art could determine the metes and bounds of the claim as excluding repetitive elements, simple repeats, or polyX repeats of low information content. However, in order to expedite prosecution, Applicants have amended claim 185 (and thus claims 189, 192, 197, 200, 221-224, 226 and 228-232 dependent therefrom) to expressly recite that what is excluded from the probes are "regions of low information content selected from the group consisting of repetitive elements, simple repeats, and polyX repeats."

Applicants submit that, as explained in the specification at page 17, line 16 through page 18, line 9, one of skill in the art as of the filing date of the present application readily could determine what is meant by the phrase "regions of low information content selected from the group consisting of repetitive elements, simple repeats, and polyX repeats," in view of common knowledge in the art and the teachings of the specification. For example, the specification teaches that such regions of low information content can be identified by use of computer programs such as the Repeatmasker program (see specification at page 17, lines 19-23). The rejection is thus obviated.

Claim 197

The Examiner contends that claim 197 is indefinite because of the phrase "probes consist of the range of 10-200 nucleotides."

Without agreeing with the Examiner that the claim is indefinite, but merely to expedite prosecution, Applicants have amended the claim in accordance with the Examiner's suggestion, replacing the phrase with "probes consist of 10-200 nucleotides." For the sake of consistency, the phrase "in the range of" has also been deleted from claims 186-188, 201, 205, 209, 213, 227. The rejection is thus obviated.

Applicants further note that the amendment of claims 186-188, 197, 201, 205, 209, 213, 227 to delete "in the range of" does not narrow the claims in any way. In particular, the claims already specify a range (*e.g.*, of 10-200 nucleotides in claim 197), and thus the deletion of "in the range of" merely removes an unnecessary redundancy in claim language.

Claim 220

Claim 220 is rejected as indefinite for depending from canceled claim 156. In response, Applicants have amended the claim to correct an editorial error in the claim dependency. Claim 220 as amended now depends from pending claim 217. The rejection is thus obviated.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, second paragraph, have been obviated and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 185, 189, 192, 197, 200, 221-224, 226 and 228-232 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the specification does not enable arrays comprising probes from which "repetitive elements, simple repeats, or polyX repeats have been excluded." In particular, the Examiner contends that these claims "broadly claim exclusion of two or more nucleotide repeats from probes," without "direction on how to exclude two or even three-nucleotide repeats."

As discussed above, Applicants have amended claim 185 (and thus claims 189, 192, 197, 200, 221-224, 226 and 228-232 dependent therefrom) to specify that what is excluded

from the probes are "regions of low information content selected from the group consisting of repetitive elements, simple repeats, and polyX repeats."

Applicants submit that one of skill in the art as of the filing date of the present application readily practice the claimed invention without undue experimentation. For example, one of skill in the art could readily identify the "regions of low information content selected from the group consisting of repetitive elements, simple repeats, and polyX repeats" using the approaches set forth in the specification at page 17, line 16 through page 18, line 9. As also explained in the specification, one program that could be used for this purpose was the Repeatmasker program (see specification at page 17, lines 19-23).

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, has been obviated and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

The Present Rejections

Claims 122, 189, 192, 197, 200, 119-222 [*sic*, presumably 221-222], 224, 226 and 228-231 are rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,329,140 by Lockhart ("Lockhart") and Bowtell, 1999, Nature Genetics Supplement 21:25-32 ("Bowtell"). The Examiner contends that claims 122, 189, 192, 197, 200, 119-222, 224, 226 and 228-231 are obvious over Lockhart in view of Bowtell. According to the Examiner, Lockhart teaches all the features of claim 122, 189, 192, 197, 221, 222, 224, 226 and 228-231 except for the feature that the genomic target sequences for a plurality of probes span a genomic region of at least 25,000 bp (Office Action at pages 8-11). According to the Examiner, Bowtell teaches microarrays that have regions of 42,000 and 30,000 gene sets, each of which is over 25,000 bp (Office Action at page 12). The Examiner concludes at page 12 of the Office Action that:

> [I]t would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Lockhart et al. by spanning genomes as suggested by Bowtell with a reasonable expectation of success. The motivation to do so is provided by Bowtell who teach the usefulness of array to span genomes and the teach of Lockhart et al. that array can span gene families (see Figure 3 and its description in column 5, lines 27-33). Thus the claimed

> invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Claim 123 is rejected as obvious of Lockhart in view of Bowtell for the reasons stated above, and further in view of Schena *et al.*, 1996, Proc. Natl. Acad. Sci. U.S.A. 93:10614-19 ("Schena"), which is said to teach microarrays to measure expression of plant genes (Office Action at page 12). The Examiner concludes on page 13 of the Office Action that:

> [I]t would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Lockhart et al. and Bowtell by targeting nucleotide sequences of plant genes as suggested by Schena et al. with a reasonable expectation of success. The motivation to do so is provided by Schena et al. who teach usefulness of microarrays in measuring plant genes and the teaching of Lockhart et al. and Bowtell who teach the usefulness of microarrays. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Preliminarily, Applicants note that claims 185-188, 190-191, 193-196, 198-219, 225, 227 and 232 (claim 220 not having been examined with respect the prior art due to the mistake in its claim dependency) appear to be clear of the prior art.

With respect to the rejected claims, Applicants respectfully submit that the rejection is error and should be withdrawn. None of the references cited by the Examiner, alone or in combination, suggests or provides motivation for the presently claimed invention. In particular, and as explained hereinbelow, Applicants respectfully submit that the Examiner has mischaracterized the teachings of the primary reference, Lockhart. Each of Lockhart, Bowtell and Schena is discussed in turn below to demonstrate that, whether alone or in combination, these references do not provide any suggestion of, or motivation for, the claimed invention.

The Law Of Obviousness

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation for* the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reach the question of whether one of

ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

"Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), abrogated on other grounds, citing to *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). In particular, the Examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). Care must be taken to avoid hindsight reconstruction by using Applicant's disclosure "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result" of the claims in question. *Grain Processing Corporation v. American Maize-Products Company*, 840 F.2d 902, 907 (Fed. Cir. 1988), citing *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983).

Applicant submits that the Examiner, in raising the obviousness rejections, is employing a hindsight reconstruction without casting his mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction cannot be used for determining obviousness. Each of the references cited by the Examiner is discussed in turn below to demonstrate that, whether alone or in combination, these references do not provide any suggestion of, or motivation for, the claimed invention.

The Presently Claimed Invention

The presently claimed invention relates to positionally-addressable ordered arrays of polynucleotide probes bound to a solid support; wherein the polynucleotide probes comprise at least 100 polynucleotide probes of different nucleotide sequences, each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, wherein the respective genomic sequences complementary and hybridizable to the probes are found at sequential sites in the genome. Importantly, the arrays are further characterized by the following features:

1. the distance between 5′ ends of the sequential sites is always less than 500 bp; and

2. the genomic sequences complementary and hybridizable to the of probes span a genomic region of at least 25,000 bp.

Feature 1 above reflects the *density* of the genomic sequences complementary to probes in the genome.

Feature 2 above reflects the *span* of the genomic sequences complementary to probes in the genome.

Thus, the arrays of the present invention contain probes that are complementary to genomic sequences that can be characterized as having a both *a high density* (due to the distance between 5′ ends of the sequential sites being always less than 500 bp in the genome) and *a large span* (due to the genomic sequences spanning a genomic region of at least 25,000 bp). The arrays of the invention allow genes which are expressed to be identified and mapped to their respective positions in the genome, and the structure of such genes (*e.g.*, intron/exon boundaries) to be determined on a fine scale (see, *e.g.*, Abstract and page 3, lines 15-27 of the specification).

As explained below, neither Lockhart, Bowtell or Schena, alone or in combination, provides any motivation for making or using arrays having both a high density and a large span.

Lockhart

Lockhart relates to identifying molecular sequence signatures in gene families using tiling arrays, and also using tiling arrays to determine whether a given gene possesses a sequence signature (Lockhart at Abstract and at column 1, lines 50-59.) The probes used in the arrays "have the sequences of the sequence signature or variations upon that sequence. Thereby, the probes define the reference sequence signature and sequences related to the sequence signature" (Lockhart at column 1, lines 63-67). The entire sequence signature is at most 300 nucleotides or 300 amino acids in length (encoded by a sequence of 900 nucleotides) (Lockhart at column 7, line 35 to column 8, line 12). The probes on the array may be tiled over the sequence signatures (column 9, line 51 through column 10, line 50) and also may contain multiple variations of the sequences signatures, some of which may

correspond to different members of a gene family (as exemplified in Figure 3 and figure legend thereto at column 5, lines 26-32). Lockhart, however, differs in key respects from the presently claimed invention, as discussed below. Specifically, Lockhart does not teach or suggest an array of probes complementary to genomic sequences having both the *high density* and *long span* of the genomic sequences complementary to the probes on the arrays of the invention.

With respect to signature sequences present in a single gene, Lockhart teaches that the signature sequences are at most 300 nucleotides or amino acids in length. Thus, although in such embodiments of Lockhart the distance separating the different sequence signatures may always be less than 500 bp, there is no suggestion in Lockhart that the probes are complementary to genomic sequences that span greater than 25,000 bases. Thus, while this embodiment of Lockhart may teach or suggest the *high density* feature of the claims, it does not teach or suggest the *long span* feature of the claims.

For probes corresponding to sequence signatures of multiple members of a gene family spread over a genome, although such probes may overall be complementary and hybridizable to genomic sequences spanning at least 25,000 bp in a single genome, there is no suggestion in Lockhart that the signature sequences to which the probes are complementary are separated by distances of less than 500 bp. Thus, while this embodiment of Lockhart may teach or suggest the *long span* feature of the claims, it does not teach or suggest the *high density* feature of the claims.

Lockhart's purpose is to interrogate for the presence of small sequence signatures of up to 300 nucleotides or amino acids. As discussed above, when the signature sequences queried are in present a single gene, Lockhart at best suggests the high density but not the long span feature of the claims; when the signature sequences queried are those of different gene family members, Lockhart at best suggests the long span but not the high density feature of the claims. There is no discernible reason, and thus no motivation, in Lockhart to create an array with a probe set having both the *long span* and *high density* features of the claims, as claimed in the present invention.

Bowtell

Bowtell is a review article of microarray technologies available for gene expression monitoring. After describing how RNA can be prepared for expression analysis (see Section

entitled "The front end – from sample to RNA" beginning on page 25), Bowtell describes how arrays are made and used (see Section entitled "Middleware: making and using microarrays" beginning on page 26). In this Section, Bowtell reviews the various arrays that were commercially available at that time. All the arrays described by Bowtell are gene expression arrays. Table 3, referred to by the Examiner, lists commercially available filter arrays, including the Affymetrix human and mouse GeneChip® arrays. It appears from the table that there is a 35K human GeneChip® array, with probes to 35,000 human genes, said probes corresponding to a total of human 42,000 genes and ESTs. In the other paragraph referred to by the Examiner, paragraph 2 in the right column of page 26, Bowtell indicates that a limitation faced by microarrays is the lack of complete genome information for organisms other than *C. elegans* and microorganisms.

Nowhere in Bowtell, including the statements referred to by the Examiner, is there provided any motivation to make or use an array having both the *density* and *span* features of the presently claimed invention. As evident from the title ("Options available – from start to finish – for obtaining expression data by microarray") and explained in the Abstract of Bowtell, the reference is directed solely to *expression* analysis. As implied by Bowtell, complex arrays containing probes for analyzing the expression of a large number of genes were desirable (see page 26, paragraph with heading "Clone Sets"; see also Table 3 referencing the 35K human GeneChip® array). However, Bowtell does not suggest the presently claimed invention. In particular, a teaching of microarrays containing probes for a large number of expressed RNAs at best suggests the *span* feature of the present claims, in that probes for thousands of expressed RNAs may be complementary to genomic sequences spanning greater than 25,000 bases, wherein such genomic sequences are exons; however, such complementary genomic sequences are not composed of the majority of genomic sequences, which majority is not present in cDNA and which majority is composed of sequences such as introns, promoter sequences, and intergenic regions. However, Bowtell in no way suggests the *density* feature of the present claims, such that the probes are complementary to genomic sequences at sequential sites that are separated by less than 500 bp, particularly since Bowtell's probes recognize only exon sequences and not the majority of genomic sequences. There is no discernible reason, and thus no motivation, in Bowtell to create an array with a probe set having the *high density* feature in addition to the *long span* feature of the claimed invention. Accordingly, Bowtell does not remedy the deficiencies of Lockhart.

Therefore, claims 22, 189, 192, 197, 200, 221-222, 224, 226 and 228-231 are not rendered obvious by Lockhart and Bowtell.

Schena

Schena does not remedy the deficiencies of either Lockhart or Bowtell. Schena is a study describing the use of microarrays containing 1046 human cDNAs, which allow the expression monitoring of 1000 human genes in parallel. In the paragraph referred to by the Examiner, Schena simply refers in the background section that a high throughput approach of "microarrays of cDNA clones as gene-specific hybridization targets [had been successful] to quantitatively measure expression of the corresponding plant genes." Schena at page 10614, left column second paragraph after Abstract.

The goal of Schena's study is to analyze in parallel the expression of as many genes as possible using the cDNAs themselves as probes. As explained in the discussion of Bowtell above, the use of arrays to monitor gene expression at best suggests arrays in which the probes are complementary to genomic sequences having the *long span* of the arrays of the claimed invention, but not the *high density*. There is no discernible reason, and thus no motivation, in Schena to create an array with a probe set having both the *long span* and *high density* features of the claims.

Accordingly, Schena does not remedy the deficiencies of Lockhart and/or Bowtell.

Conclusion Regarding Obviousness

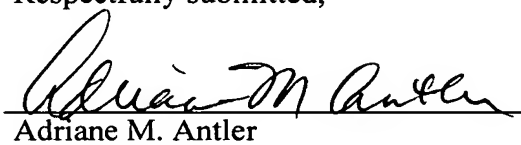
In view of the foregoing remarks, it is submitted that the obviousness rejection is in error and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

Respectfully submitted,

Date: February 14, 2007



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Enclosures